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Indoor Air Quality in Asia

Proceedings of the International Conference held at the Central Plaza Hotel, Bangkok, Thailand on 28-29th November, 1991.

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Edited by

B. R. Reverente Jun
Philippine Refining Co Inc
1351 United Nations Avenue
Manila
PO BOx 1176
Philipppines

D. F. Weetman
School of Health Sciences
University of Sunderland
Sunderland
England

and

M. Wongphanich
Occupational Health Department
Faculty of Public Health
Mahidol University
420/1 Rajvidhi Road
Bangkok 10400
Thailand

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A CRITIQUE OF THE METHODS USED TO ASSESS THE TOXIC EFFECTS ON MAN OF COMBUSTION PRODUCTS.

D. F. WEETMAN

School of Health Sciences, University of Sunderland , Sunderland, Tyne and Wear, England

Key Words: combustion products, epidemiology, risk assessment, environmental tobacco smoke, cardiovascular diseases.

ABSTRACT

Combustion of organic material results in the release of particles, gases, and pyrolytic products, all of which can accumulate in the indoor environment, and could damage health. The methods of assessing risk to man are reviewed, and it is concluded that epidemiology provides the best single approach. The problems in interpretation of epidemiological studies are reviewed, with particular emphasis on the specific problem of environmental tobacco smoke (ETS) and cardiovascular disease. It is concluded that too many important potentially confounding factors have been overlooked to decide if there is an association between exposure to ETS and cardiovascular diseases.

NATURE AND SOURCE OF COMBUSTION PRODUCTS

It is difficult to imagine life without combustion. In addition to domestic heating, combustion of some form of fuel occurs in cooking, many forms of transportation, most industrial processes and most of the generation of electrical power. The common factor is that some form of fuel is burnt, and the fuel is derived from organic matter, with the inevitable release of pollutants. Not all combustion contributes pollutants to the indoor environment, but in those situations where this effect appears to be minimal, it should be remembered that the indoor air is derived from that outdoors, so the dirtier the air outside a building, the more polluted it will be inside.

When organic matter is burnt, three classes of pollutant are formed. First there are gases. As the predominant chemical process is oxidation, which usually occurs without sufficient oxygen to allow complete oxidation, there is the release of a complex mixture of oxides. Thus amongst the gases generated by combustion, there are oxides of carbon, nitrogen and sulphur.

Organic molecules can undergo complex re-arrangements without the consumption of oxygen in a process called pyrolysis, which is largely determined by the temperature of combustion. Finally, there is the generation of particles, which are the small globules of organic matter that give rise to the visibility of smoke. Particles vary in size, and undergo complex changes in shape and surface area when they cool down to the ambient temperature. Large particles do not stay suspended in the air for long. Particles up to 10μm are readily inhaled and may not be rapidly cleared by from the lung; large particles (10μm aerodynamic diameter) are deposited in the upper respiratory tract, whereas small ones (0.1μm) are exhaled [1]. The important aerodynamic diameter with respect to potential pulmonary toxicity is probably about 0.5μm [1]. Much the same mixture of gases, pyrolytic products and particles are generated from the combustion of any organic matter. For example, there is more similarity than difference in the products released from burning wood and tobacco. With combustion of organic matter that has undergone some degree of metamorphosis, as with coal, oil and natural gas, there is variation in the proportions of components generated from each, but again there is a mixture of gases, pyrolytic products and particles.

METHODS OF RISK DETERMINATION

The purpose of determining the risk to man from combustion products arises from the ubiquitous distribution of these substances. Scientific knowledge is sought because of man's insatiable curiosity, but increasingly scientists have to justify the funds they consume, so there need to be an acceptable purpose of the investigations. Any reliable findings about risks to the health from combustion products can be used in attempts to regulate levels of the offending substances, and thus protect man.

Laboratory Studies

Laboratory animals can be exposed to smoke and then assessed for any effect. However, this type of experimentation is fraught with difficulty. There is always some carbon monoxide generated by combustion, which prevents high doses of smoke being administered. The anatomy of the respiratory system of, say, rats is quite different from that of man, so it is difficult to predict the outcome in this latter species from effects seen in the former. Any experience of pharmaceutical research teaches that there is no completely reliable way of translating effects seen in laboratory animals to man. To determine what happens in man, it is necessary to investigate in man.

Direct experimentation in man can be achieved in exposure chambers. The problems here are that exposure must be short-term, and there is still an upper

limit to the dose that can be tested due to the presence of carbon monoxide. Of course, it is possible to separate the various chemicals in smoke, and apply them to volunteers in exposure chambers, either individually, or in defined mixtures, but then it is barely possible to measure any interactions between the different components. Any reduction in the scale of the test system, for example by administering smoke to tissue cultures, still involves an extrapolation from the *in vitro* system to intact man. The experimental methods available are inadequate for this purpose.

Epidemiology

It is possible to measure the effects of long-term exposure of man to combustion products by epidemiological techniques. With this approach, a population of exposed individuals is identified and the rate of any medical outcome in this group is compared with that in a suitable control group. Two study designs are possible. First, one can either start by identifying individuals with a condition (i.e. cases) and attempt to show a greater exposure in the past to the suspected cause than occurs in a demographically matched control group. The second approach is to assemble a population (i.e. cohort) of individuals and determine what happens to them medically over several years. The cohort method does not provide rapid answers, especially with the most frequent causes of death, which frequently have a slowly developed pathology. Table 1 summarises the problems associated with such studies.

Table 1 Problems in Epidemiology

1.	Selection of exposure and control groups
2.	Multifactorial nature of disease
3.	Difficulty in controlling confounding variables
4.	Only associations detected
5.	Intervention studies are difficult

The best way to understand the difficulties of such epidemiological investigation is to examine the quality of the evidence in a specific case. As the regulators are currently considering the health effects that may result from exposure to environmental tobacco smoke (ETS), this will serve as an appropriate example. The latest claims are that ETS is causally related to ischaemic heart disease, so the quality of this evidence will be considered in detail. However, the investigator is confronted by comparable difficulties with combustion products from any fuel source.

Study Design

The study design is shown in figure 1. The exposed group are obtained by selecting non-smokers who are married to smokers, whereas non-smokers married to non-smokers provide the unexposed group. The rationale of this design is that the non-smokers (usually wives) would be exposed to ETS in the home from the smoking of their spouses. With these two populations, it is possible to compare the rates for ischaemic heart disease, either in case-control or cohort studies. The problems of interpretation arise from the imprecise distinction between the two exposure groups, and because there is no allowance made for exposure to ETS outside the home. A second difficulty is the determination of the smoking status of the spouse, which is usually achieved from the response of individuals to questionnaires. Any wrongly classified partners tends to reduce the precision of the study.

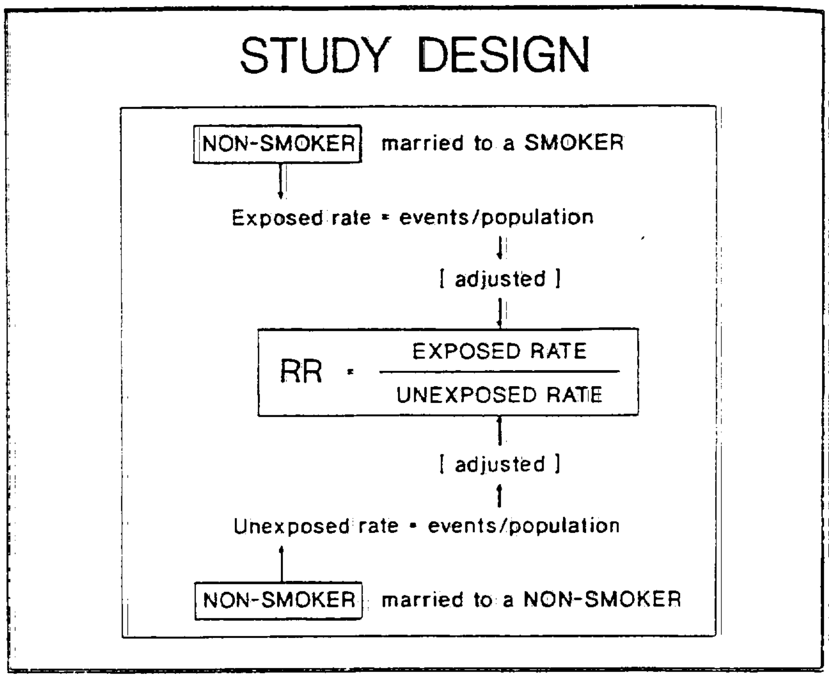

Figure 1.

A quite different set of problems relate to the definition of an effect, i.e. those who have the disease. If one relies on death certificate information, then the fact that the individual has died is reliable, but the cause of death is prone to error [2]. As few autopsies are now performed in most countries of the world (for example, currently, less than 13% of bodies in the USA are subjected to autopsy [3]), the cause of death has to be deduced from the signs and symptoms of the patient alone.

If the possible causes of ischaemic heart disease are considered, medical scientists do not have an unequivocal answer. This has resulted in a sort of second level approach, where risk factors apparently predisposing individuals to cardiovascular disease are identified. In other words, the aetiology of cardiovascular disease is considered to be multifactorial. To date, over 200 such risk factors have been proposed by various research groups [4] (not all medical scientists agree with this approach: McCormick and Skrabanek [5] have suggested that we should refer to risk markers, as opposed to risk factors, so as not to confuse association with causation). However, if there are constitutional or behavioral characteristics of individuals that could predispose them to cardiovascular disease, each one should be controlled for in epidemiological studies, otherwise they may act as confounders, allowing an incorrect conclusion to be reached.

Much of the interest in ETS and cardiovascular disease arises from a review by Glanz and Parmley [6], in which the authors presented a case that ETS was responsible for a proportion of the cases of the disease. Nine epidemiological studies were identified in the literature (5 with a statistically significant effect, supposedly from spousal exposure [7-11]), and 4 without [12-15], which allowed Glantz and Parmley to conclude "These epidemiological studies demonstrate a connection between ETS exposure and death from heart disease." One other study [16] has been added to the ones covered by Glanz and Parmley.

Table 2 contains a summary of the epidemiological studies linking ETS with cardiovascular disease. The medical endpoint varies from study to study, and contains both "death from" and "possession of" the specified condition; the following conditions were taken as the endpoint: ischaemic heart disease, arteriosclerotic heart disease, coronary heart disease, myocardial infarction, stroke, and all cardiovascular diseases. The reliance on death certificate information as the medical endpoint is also indicated in table 2.

Table 2 The Epidemiological studies of ETS and cardiovascular diseases.

STUDY	REFERENCE	DISEASE	END POINT	TOTAL EVENTS	TESTS sig/total
BUTLER	[12]	CHD	D.C	64	0/1
HIRAYAMA	[10]	IHD	D.C.	494	1/3
GARLAND	[13]	IHD	D.C	19	0/10
LEE	[15]	IHD + STROKE	DIAGNOSIS	121	0/30
SVENDSEN	[11]	CHD	PANEL	13	2/17
HE	[8]	CHD	DIAGNOSIS	34	24/47
HELSING	[7]	AHD	D.C.	2014	10/22
HOLE	[9]	IHD	D.C + PANEL	84	1/5
HUMBLE	[14]	All CVD	D.C.	76	0/24
DOBSON	[16]	MI	D.C. + PANEL	382	2/12

Under EVENTS, the numbers refer to those in the CONTROL + EXPOSED groups for the cohort studies, and the number of cases in the case-control studies, and give an indication of the ability of the tests to detect an effect. The values are for males and females combined, and both home and work place exposure to ETS.

IHD = ischaemic heart disease
CHD = coronary heart disease
AHD = arteriosclerotic heart disease
MI = myocardial infarction
CVD = cardiovascular disease
D.C. = death certificate
PANEL = evidence reviewed by a panel of experts
DIAGNOSIS = disease determined by standard diagnostic techniques

The large number of comparisons made in the papers is indicated in Table 2. When multiple comparisons are made on one set of data, the comparisons are not truly independent (some values will be used and then re-used in different tests), so <u>any</u> study containing a statistically significant outcome will be considered further. The positive studies are re-considered in Table 3.

It has already been stated that cardiovascular diseases are thought to be multifactorial in their aetiology, so any putative causes other than exposure to ETS that are not controlled for will be capable of confounding the epidemiological studies. For this reason, some of the best established risk factors for cardiovascular diseases have been identified from the literature (Table 4), and the extent of the control over these potential confounders has been determined (Table 3).

Table 3 Missing
epidem

STUDY
HIRAYAMA [10]
SVENDSEN [11]
HE [8]
HELSING [7]
HOLE [9]
DOBSON [16]

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RISK FACTOR
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Cigarette smoking
Dietry fat load
Diabetes
Lack of exercise
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Table 3 Missing evidence (potential confounding variables) in the positive epidemiological studies

STUDY	Obesity	Hypertension	Alcohol	Fatty Diet
HIRAYAMA [10]	NO	NO	YES	NO
SVENDSEN [11]	YES	YES	YES	YES
HE [8]	YES	YES	YES	YES
HELSING [7]	NO	NO	NO	NO
HOLE [9]	YES	YES	NO	YES
DOBSON [16]	NO	NO	NO	NO

In no study was the following controlled for: diabetes, exercise and menopausal status in women. Family history of cardiovascular disease was not controlled for, except in the study by He et al [8]. The Svendsen et al study [11] was the only one to employ a marker to detect smoking behaviour.

Table 4 The best established cardiovascular risk factors

RISK FACTOR	SELECTED REFERENCES
Family history of disease	[18, 19, 20]
Hypertension	[21, 22]
Cigarette smoking	[17, 22]
Dietry fat load	[22, 23]
Diabetes	[18]
Lack of exercise	[24, 25]
Menopausal status	[18, 26, 27]
Alcohol consumption	[4]
Obesity	[28]

From table 3 it is apparent that the epidemiological studies are not all of the same standard. Perhaps the best designed study was that performed by Svendsen et al [11]. This was the only study that attempted to confirm the exposure to ETS by measuring a marker of exposure (serum thiocyanate concentration). The potential confounders of hypertension, body weight, dietary fat intake and alcohol consumption were all controlled for, but the population selected for study was atypical. The subjects were from the 15% of the U.S. population thought to be at greatest risk from cardiovascular disease. The cardiovascular disease risk factors considered to be important in this study were high blood pressure, cigarette smoking and high blood cholesterol levels, and those most at risk possessed two of the three risk factors. When it came to any effect of ETS, this was measured in non-smokers by the spousal smoking

status method. Thus all ETS exposed subjects must have been both hypertensive and had high blood cholesterol levels. However, 3 really important cardiovascular disease risk factors (family history of cardiovascular disease, glucose tolerance and whether or not the subjects exercised) were not controlled for. The final point that needs to be made from this well-designed study was that exposure to ETS was not associated with possession of a cardiovascular disease in a statistically significant manner: the significant result that qualifies it for examination in Table 3 was between surrogate exposure to ETS and death from all causes.

The two studies that provided the highest proportion of statistically significant associations between ETS exposure and death from cardiovascular disease were by Helsing and others [7] and by He et al [8]. The study by Helsing et al was the least well controlled of all the studies considered here. There was no attempt to confirm exposure to tobacco smoke (either from ETS or undisclosed smoking). No information was reported about blood pressure, body weight, dietary fat intake, alcohol consumption, family history of cardiovascular disease, glucose tolerance, exercise, and menopausal status of the female subjects. In fact this study is best considered to be a linking of death certificate information to the response to a self-administered questionnaire. When one considers the absence of control over potential confounders, no reliance can be placed on the findings.

The case-control study from China [8] has only been published in Chinese, but the 34 female coronary heart disease patients were shown to be at risk from spousal smoking (OR = 3.52, confidence limits, P = 0.05, 1.26 - 7.17). This remarkable level of risk greatly exceeds many estimates of the direct effects of smoking [9, 17]. The effects of potential confounding influences was assessed in a multivariate logistical regression analysis, where it was shown that the effects of surrogate exposure to ETS persisted when the following risk factors were controlled for: previous history of hypertension, family history of hypertension, family history of coronary heart disease, history of passive smoking, amount of exercise, and previous history of hyper-cholesterolaemia. However, this study on a small group of only 34 patients needs to be extended, evidence of the effects of direct smoking determined, and evidence of difference in diet between the cases and controls added.

The quality of the other studies considered here lie between those of Svendsen et al and Helsing et al. All are poorly controlled. A study of appropriate standard and size has not yet been performed, so it is not yet possible to decide whether or not there is an association between exposure to ETS and cardiovascular disease. The fundamental problems in study design consist of:

a: the selection of the exposed and control groups;

b: the exact classification of disease; and

c: the exercise of adequate control over the numerous potential confounding variables. Much the same difficulty arises with any attempts to examine the

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1.	The association less than 3 [29]
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possible association between combustion products and common diseases.

Table 5 To progress from the association of an environmental factor with a medical outcome to establishing causality, several steps have to be taken. The whole of the evidence should conform to the following criteria.

1.	The association should be strong enough to be persuasive: it is seldom the case with RR less than 3 [29].
2.	There should be consistency of findings between different studies.
3.	The effect should be specific, or as near to this as possible, with the exposed group.
4.	The temporal relationship with respect to exposure should be appropriate to the pathological sequence of the disease.
5.	There should be a dose-response relationship, whereby the greater exposures result in more cases than occurs in the less exposed group of individuals.
6.	There should be a "freedom from implausibility" with respect to biological mechanisms.
7.	All the evidence should be coherent and point towards one conclusion.

In virtually all cases, the full set of criteria are not fulfilled, but the nearer one is to achieving this, the more persuasive is the argument. (Adapted from [2].)

If one were able to show a statistically significant association between combustion products and disease in an epidemiological study, as is the case with the case-control study from China [8], it is still not evidence that the products cause the disease. Association is only association: to conclude that exposure causes the condition, further steps are needed. Table 5 indicates some of the properties of an association that would have to be demonstrated before causation can be concluded. It should be noted that there is much debate amongst epidemiologists as to the exact criteria for taking this further step. In all cases, there is an element of subjectivity in reaching the decision that the outcome is caused by the influence studied.

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